which provides data which demonstrate that the methods described in the specification enable one of ordinary skill in the art to make a transgenic animal.

In *Hybridtech Inc. v Monoclonal Antibodies Inc.* 802 F.2d 1367, 1385 (Fed. Cir. 1986), the court held that there was a failure to meet the enablement requirement because the application failed to disclose any specific starting material or the conditions under which the claimed process could be carried out. In sharp contrast, the Applicants' disclosure specifically states that a dominant negative allele of a mismatch repair gene (starting material) can be microinjected into fertilized eggs which can then be implanted into pseudopregnant females which have been prepared to accept such eggs by hormone treatments (conditions). Page 9, lines 21-28. Other alternatives for making transgenic animals are also provided. Page 9, line 29 – page 10, line 5. Moreover, many specific methods of microinjection and subsequent implantation were well-known in the art at the time of filing. The Office Action acknowledged the art of making transgenic animals, but asserted that the state of the art was unpredictable. The factual evidence provided in the declaration of Dr. Kline, however, indicates that transgenic animals according to the invention can be made by following the teachings of the specification.

The Patent Office addresses several specific concerns in the rejection involving the use of the transgenic animals. First, the Patent Office suggests that even if a skilled artisan could make a transgenic mouse, he would not know how to use the transgenic mouse. Second, the Patent Office suggests that the transgenic animals would have their own intrinsic full-length *PMS2* in addition to the mutant form and speculates whether the rate of repair would "increase in any and all cells of the animal or a particular cell." Third, the Patent Office questions what effect the expression of a dominant negative form

of a mismatch repair gene would have on metabolism and phenotype of animals. The Patent Office points to examples in which targeted gene mutations have different effects in animals with different genetic backgrounds. The Patent Office concludes by stating that in the absence of any predictable phenotype, the skilled artisan would not know how to use the transgenic animals. Each of these will be addressed in turn.

The Applicants have discovered that a dominant negative form of a mismatch repair gene, when expressed, overrides the intrinsic mismatch repair process in cells. The result is that the cells cannot repair mismatched base pairing of DNA that normally occurs during cell replication and division, despite the presence of a normal copy of the mismatch repair gene (see the Applicants' specification at page 7, lines 1-12). The end result is that cells accumulate mutations, in a random fashion, throughout their genome. Thus, mutations may affect particular endogenous genes of interest in animals that harbor a dominant negative allele of a mismatch repair gene.

One of ordinary skill in the art would clearly recognize the utility of animals that would spontaneously and randomly accumulate mutations in genes of interest. Such animals will accumulate gene mutations that may be silent or have an effect on the phenotype of the animal. Such mutations can be studied *in situ* without the need for laborious procedures such as targeting mutations and making transgenic animals using constructs for each and every targeted mutation construct. The rapid generation of mutations in genes of interest is a tremendous asset to the skilled artisan. It obviates the need for chemical mutagens or radiation (which may cause secondary effects on the animals and laboratory personnel). Further, it permits the mutagenesis of both endogenous genes and genes the artisan introduces into the transgenic animal.

The specification itself provides the skilled artisan with guidance and suggestions for use of the transgenic animals. See page 10, lines 7-24. The specification further describes a human family having a dominant negative form of a mismatch repair gene. Page 23, line 23. Two of the children developed tumors at a young age, evidencing that accumulated mutations affected normal cell growth in these children. The genes of these children could be studied to determine tumorigenic mutations in tumor-associated genes of interest, for example.

The Patent Office speculates that since the transgenic animals may have their own, endogenous, full-length *PMS2* in addition to the mutant form, that the rate of repair might "increase in any and all cells of the animal or a particular cell." However, the Specification clearly teaches that a dominant negative allele impairs mismatch repair even in the presence of the wild-type allele. Page 7, lines 1-2. Thus, this speculation is in direct opposition to the applicants' explicit teachings.

The Patent Office implies that the claims encompass introduction of a wild-type allele of a mismatch repair gene. Office Action at page 5, lines 9-11. However, each of the claims refers to a "dominant negative allele." Thus, the claims cannot read on use of a wild type allele.

Finally, the Patent Office questions the effect of the dominant negative allele on metabolism or phenotype. This is clearly addressed in the specification. The Specification describes that the expression of the dominant negative allele inhibits mismatch repair activity, causing the cells in the animal to accumulate mutations at an abnormally high rate (*i.e.*, the cells become "hypermutable") (see the Specification at page 7, lines 7-9). This is evident in the human family possessing the dominant negative

allele of PMS2, described in the specification at page 23, line 23-line 30. The phenotype of hypermutability in the children evidenced itself in the early onset of tumors. Moreover, the Specification describes reliable indicators of the change in phenotype at page 10, lines 15-24 teaching various assays that enable one of skill in the art to assess mutagenesis. Applicants earnestly submit that the claims are fully enabled by the Specification.

The Patent Office further rejects the claims under the Written Description Requirement of 35 U.S.C. § 112, stating that the specification does not describe an animal comprising a protein that comprises the first 133 amino acids of the PMS2 protein, or any PMS2 gene, and does not disclose identifying characteristics of the species, a representative number of species, or the sequence of the mismatch repair genes encompassed by the claimed invention. The specification, however, clearly discloses that the transgenic animals of the invention may express a dominant negative form of a mismatch repair gene at page 7, lines 28-31. The Specification teaches that the dominant negative allele produces a phenotype whereby mismatch repair is disrupted, leading to hypermutability and states any gene which produces this effect may be used. Page 7, lines 1-12. This, of course includes, and the specification specifically mentions, the PMS2 truncation mutant PMS-134. Contrary to the assertions of the Office Action, the sequence of the PMS2 gene is provided as SEQ ID NO:1, and the Specification clearly teaches the sequence of the PMS-134 mutant by stating that the PMS-134 mutant DNA sequence terminates after the 133rd amino acid of PMS2. Page 7, lines 5-7. Moreover, the declaration of Dr. Kline provides factual evidence that the inventors were in constructive possession of the invention at the time of filing, as the Kline data were

obtained following the teachings of the specification. Applicants earnestly submit that the specification conforms to the Written Description Requirement.

Applicants earnestly submit that the claims are enabled by the specification. This is supported by the factual evidence provided in the declaration of Dr. J. Bradford Kline. Dr. Kline demonstrated that following the teachings of the specification, transgenic animals were produced expressing a dominant negative form of a mismatch repair gene, and that it was transmitted in the germ line. Applicants request allowance of the claims.

Respectfully submitted,

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